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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,834	02/16/2006	Jonathan Michael Blackburn	40418-508N01US	8870

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EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1656	

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12/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,834	BLACKBURN ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-42,44-77,79 and 80* is/are pending in the application.

4a) Of the above claim(s) *45-70 and 72-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-42,44,71,79 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/20/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received September 18, 2009.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Claims 1-39, 43, 78, 81 are canceled. Claims 45-70, 72-77 are withdrawn. Claims 40-42, 44, 71, 79-80 are currently under examination.

Priority: Applicants' request for priority to UK 0224872.2, filed October 25, 2002, is acknowledged.

Objections and Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40-42, 44, 71, 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thinakaran (US 20030022151; IDS 05.28.09, previously cited) in view of Takagi et al. (US 4610962, previously cited). Thinakaran discloses a method for screening zeocin resistance in cells expressing a PS1 chimeric polypeptide (p. 21-22 [0248-0252]). A PS1 chimeric polypeptide comprises presenilin fused to a YFP (yellow fluorescent protein) and Sh ble (a ble marker protein) (p. 19 [0221]). Thinkaran further disclose that the antibiotic resistance gene (Sh ble) confers antibiotic resistance by stoichiometrically binding to an antibiotic (abstract). The

antibiotic screening can be used to detect changes in the levels of unstable chimeric proteins (abstract). Thinkaran discloses assays that measure binding of a molecule to said chimeric protein such that binding of a molecule to the chimeric protein may stabilize the protein (p. 9 [0105]). For the *in vitro* assays, Thinkaran discloses that the protein may be either free in solution, fixed to support, or expressed in or on the surface of a cell (p. 9 [0105]). However, Thinkaran does not explicitly teach zeocin is immobilized onto a surface.

Takagi et al. (US 4610962) disclose carriers for immobilizing physiologically active substances (abstract). Takagi et al. also disclose that the immobilized carriers can be used in assays for detecting proteins (col. 7 lines 8-28). Takagi et al. disclose antibiotics, including bleomycin, are substances that can be immobilized onto the surface of the carriers (col. 2-3 lines 52-5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Thinakaran et al. by immobilizing zeocin onto a surface as suggested by Takagi et al. for screening and/or assessing the binding of a chimeric protein comprising a fluorescent marker and a Sh ble protein marker in an *in vitro* assay for determining protein binding (claims 40-42, 44, 71, 79). It would be reasonable for one of ordinary skill to know that the binding of said chimeric protein to said zeocin would mean that said chimeric protein was properly expressed.

Regarding the instant limitation of detecting a protein expression and folding, it should be noted that the correct conformation and/or folding of the Sh ble-YFP fusion protein would naturally occur since Thinkaran discloses that the antibiotic (i.e. zeocin) binds to said protein. While the method of Thinkaran et al. in view of Takagi et al. may not explicitly disclose

detecting protein expression and folding, the active steps of the instant invention are within the scope of the method of Thinkaran et al. in view of Takagi et al.; therefore, even if the active steps of the instant invention are used for a different purpose does not alter the conclusion that its use in the prior art would be prima facie obvious from the purpose disclosed in the references. See also In re Lintner, 458 F.2d 1013, 1018, 173 USPQ 560, 562 (CCPA 1972). MPEP 2100.

It would also be reasonable for one of ordinary skill to know that said chimeric protein can be purified from the cells after expression since these skills and techniques are routine in the art and readily used in screening assays for proteins and molecules (Thinakaran p. 17 [0207]; claim 40, 71).

While Takagi et al. do not disclose detection by mass spectrometry, Applicants are again reminded that mass spectrometry is a method known in the art that can be used to quantify proteins; therefore, it would be reasonable for one of ordinary skill to know that any suitable and/or appropriate protein detection method can be used to assess protein binding to a molecule, i.e. antibiotic (claim 79).

In their remarks, Applicants assert that (1) the assay disclosed in Thinakaran is an *in vivo* cell viability assay (see page 22 [0252]) that exploits the antibiotic resistance properties of a bleomycin resistance gene (see e.g. page 4 [0049]). In contrast, the claimed in vitro screening method requires a cellular lysate. Moreover, although Thinakaran discloses that an antibiotic resistance gene confers antibiotic resistance by stoichiometrically binding to the antibiotic, the significance of this statement is solely that stability of the protein to which the resistance protein is fused may be determined by correlating the amount of expression of resistance protein with

the concentration of antibiotic required to kill the cells. It in no way suggests using the binding of the Ble resistance protein to bleomycin in an affinity capture system using cellular lysates, which is required by the claims. (2) The *in vitro* binding assays mentioned at page 9 [0105], referred to by the Examiner, look at the interaction between a candidate modulator and an unstable protein. This section is concerned solely at looking at the ability of candidate modulators to bind to a target molecule. Although Thinakaran mentions that the unstable protein may be labeled, there is no suggestion of labeling the protein with an antibiotic resistance gene. The *in vitro* binding assays disclosed in this section do not suggest the claimed invention in any way. There would have been no motivation to adapt Thinakaran's *in vivo* cell viability assay, which uses the antibiotic resistance properties of the bleomycin resistance gene, to the claimed *in vitro* solid support binding assay, which utilizes the binding properties of the bleomycin resistance gene. (3) Takagi does not overcome the deficiencies of Thinakaran. Takagi discloses a carrier comprising an assembly of regenerated cellulose fibers on which a physiologically active substance is immobilized (see e.g. abstract and col. 5 lines 57-58). There is no suggestion of using the carrier to detect protein expression and folding. Neither is there any suggestion of using the carrier to bind to the tagged portion of a fusion protein, let alone to the Ble marker portion of a fusion protein. Applicant's arguments have been fully considered but they are not persuasive.

(1) Reply: Firstly, it should be noted that a 103(a) reference must be considered in its entirety (MPEP 2141.02). Thinakaran discloses the use of *in vivo* cell viability assays (p. 22 [0252]), however, Thinakaran also discloses the use of *in vitro* assays. The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these

alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed.." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). In this instance, it would be reasonable for one of ordinary skill to translate the use of an *in vivo* assay to an *in vitro* assay because Thinakaran discloses that both types of assays can be used to detect labeled proteins.

Regarding Applicants' remarks that the instant invention provides a "cellular lysate", it should be noted that Thinakaran discloses that *in vitro* assays generally use isolated molecules and can be run quickly and inexpensively (p. 9 [0104]). Therefore, it would be reasonable for one of ordinary skill to know that a biological sample comprising the expressed chimeric protein, i.e. cellular lysate, can be used to contact a surface with the immobilized zeocin antibiotic. One of ordinary skill would know that it is obvious to translate the *in vivo* assay disclosed in the working example (p. 22 [0252]) to an *in vitro* assay (p. 9 [0103-0106]) since both assays can be used to bind a chimeric protein labeled with a Sh ble marker.

Further, the recitation "detecting protein expression and folding" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In this instance, upon detecting the binding of said chimeric protein to said zeocin in the assay, it would naturally flow that said chimeric protein was properly expressed and proper folding occurred.

(2) Reply: Thinakaran discloses that the protein is usually the labeled species in *in vitro* assays (p. 9 [0105]). On pages 7-8, Thinakaran discloses fusion protein comprising a fluorescent marker and an antibiotic resistance marker. Therefore, it would be reasonable for one of ordinary skill to use an antibiotic resistance marker, i.e. Sh ble. Additionally, as already noted above, Thinakaran discloses an actual working example of a protein labeled with an antibiotic marker, i.e. a PS1 chimeric polypeptide comprises presenilin fused to a YFP (yellow fluorescent protein) and Sh ble (a ble marker protein) (p. 19 [0221]).

(3): Reply: Firstly, it should be noted that the Takagi et al. reference was cited to note that it is known in the art that antibiotics can be immobilized onto a surface. Therefore, since Thinakaran discloses that labeled proteins, in a solution, can be detected in an *in vitro* assay, it would be reasonable for one of ordinary skill to know that an antibiotic can be immobilized on a surface in a binding assay that detects said labeled protein.

See also remarks in the reply sections of (1) and (2).

For at least these reasons, the 103(a) rejection is maintained.

Claim 80 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thinakaran (US 20030022151, previously cited) in view of Takagi et al. (US 4610962, previously cited) in view of Calmels et al. (1993 Molecular Pharmacology 44: 1135-1141; previously cited). The teachings of Thinakaran et al. in view of Takagi et al. are outlined above. Thinakaran et al. in view of Takagi et al. do not teach a labeled antibiotic.

Calmels et al. disclose a fluorescently labeled antibiotic and that the protein product of the Sh ble gene binds to an antibiotic (bleomycin) with 1:1 stoichiometry (p. 1135).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Thinakaran et al. in view of Takagi et al. by substituting the fluorescently labeled antibiotic of Calmels et al. for the unlabeled antibiotic of Thinakaran et al. in view of Takagi et al. (claim 80). The motivation to do so is due to one of ordinary skill in the art's desire to generate a stronger visualization signal upon the protein binding to the antibiotic.

The reasons for maintaining the 103(a) rejection over claim 80 is the same as noted above.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maryam Monshipouri/

Primary Examiner, Art Unit 1656

December 2, 2009

Marsha Tsay
Art Unit 1656